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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,280	02/11/2002	Karin Herbers	3557-9	9827

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EXAMINER	
KALLIS, RUSSELL	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,280	HERBERS ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 6-7 and 10 rejected under 35 U.S.C. 102(b) is withdrawn in view of Applicant's amendments.

Claims 1-18 are cancelled. Claims 19-43 are pending and examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for the reasons of record set forth in the Official action mailed 12/30/2004. Applicant's arguments filed 7/05/2005 have been considered but are not deemed persuasive.

The claims are broadly drawn to methods of promoting the biosynthesis, production of, or improving the production of tocopgerol in transgenic plants by inhibition of the expression of homogentisate dioxtgenase using an anti-HGD homogentisate dioxygenase, an antisense of a nucleic acid sequence motif of SEQ ID NO: 1, or an antisense nucleic acid that hybridizes to a nucleic acid sequence motif of SEQ ID NO: 1, and plants transformed thereby and seeds of said plants.

Applicant describes a recombinant vector encompassing an expression cassette comprising a antisense fragment of 575 bp (SEQ ID NO: 1) isolated from *Brassica napus* using *Arabidopsis* specific HGD primers; and incorporates through reference polynucleotide sequences encoding homogentisate dioxygenase (HGD) enzymes from human, mouse and *Arabidopsis* on page 15 lines 41-44.

Applicant does not describe an anti-HGD sequence other than the sequence that is complementary to SEQ ID NO: 1 or an HGD sequence motif in accordance with SEQ ID NO: 1.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of anti-HGD homogentisate dioxygenase nucleic acid sequences or HGD sequence motifs. Applicants only describe SEQ ID NO: 1 a 575 bp fragment isolated from *Brassica napus* using *Arabidopsis* specific HGD primers and incorporate through reference HGD encoding sequences from human, mouse and *Arabidopsis*. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of HGD encoding polynucleotides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for HGD activity or those nucleic acid sequences that are anti-

HGD sequences, it remains unclear what features identify HGD sequence motifs or anti-HGD homogentisate dioxygenase nucleic acid sequences. Since the genus of anti-HGD homogentisate dioxygenase nucleic acid sequences has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

Applicant asserts that one of ordinary skill could recognize structural features common to the members of the genus of HGD sequences and present an alignment of HGD sequences from brassica napus, Arabidopsis thaliana, Homo sapiens and Mus musculus (response page 12). Applicanr further states that the skilled artisan would understand possession based upon the conserved areas of the genes.. when they match accessible regions of the target DNA (response page 12). Applicant has not described which conserved areas of the HGD gene or which areas in general would be accessible regions of the target RNA molecule to sufficiently describe the broadly claimed genus of anti-HGD homogentisate dioxygenase nucleic acid sequences.

Claims 19-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vector encompassing an expression cassette comprising an antisense homogentisate dioxygenase nucleic acid sequence of SEQ ID NO: 1 operably linked to a plant specific promoter or the 35S promoter and a OCS terminator, and a microorganism and transformed plant comprising said vector, and a method for generating transformed *Brassica napus* plants therewith, does not reasonably provide enablement for a vector encompassing an expression cassette comprising any anti-HGD homogentisate dioxygenase nucleic acid sequence operably linked to a plant specific promoter or the 35S promoter and a OCS terminator other than a vector comprising the antisense sequence of SEQ ID NO: 1; or any method of making any transformed plant using any anti-HGD sequence other than a method making a transformed

Brassica napus plant using a vector comprising the antisense sequence of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is maintained for the reasons of record set forth in the Official action mailed 12/30/2004. Applicant's arguments filed 7/05/2005 have been considered but are not deemed persuasive.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are broadly drawn to a vector encompassing an expression cassette comprising an anti-HGD homogentisate dioxygenase nucleic acid sequence operably linked to a plant specific promoter or the 35S promoter, a microorganism comprising a vector encompassing an expression cassette comprising an anti-HGD homogentisate dioxygenase nucleic acid sequence, plants transformed with either the said vector or said microorganism comprising the said vector; and a method of transformation using said anti-HGD homogentisate dioxygenase nucleic acid sequence.

Applicant teaches transformation of *Brassica napus* with a vector comprising SEQ ID NO: 1, an antisense fragment isolated from *Brassica napus* cDNA library using PCR primers derived from an *Arabidopsis* HGD encoding polynucleotide sequence (pages 15-20 of the specification).

Applicant does not teach expression cassettes, vectors or plants comprising anti-HGD homogentisate dioxygenase nucleic acid sequences or HGD sequence motifs other than the antisense sequence of SEQ ID NO: 1 for generating transformed *Brassica napus* plants.

The state-of-the-art is such that one of skill in the art cannot predict which unspecified anti-HGD homogentisate dioxygenase nucleic acid sequences in sense or antisense orientation or what other types of on-exemplified anti-HGD sequences comprising unspecified polynucleotide (having an HGD motif or not) would be capable of inhibiting homogentisate dioxygenase activity when expressed in a plant because most binding sites that are vulnerable to an antisense sequence, including ribozymes and external guide sequences are inaccessible (Branch *et al.* TIBS, vol. 23, Feb. 1998, pp. 45-50; page 49 column 2 lines 26-34), and thus the power of discrimination of an antisense fragment is unpredictable. Branch *et al.* sums up the challenges and unpredictability to finding effective antisense molecules. Branch teaches while antisense strategies look easy on paper, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven due to unexpected non-antisense effects and blocked internal structures rendering most potential binding sites inaccessible to antisense molecules (*ibid.* p. 45). Thus, absent clear and specific information in the specification regarding the identity and structure of each anti-HGD nucleic acid sequence encompassed by the claims; and that each anti-HGD sequence would play a role in

homogentisate dioxygenase activity, one skilled in the art would not be able to make anti-HGD nucleic acid sequences with predictability. Similarly, not only for antisense, ribozymes, and external guide sequences, but the category of anti-HGD sequences also comprises sense co-suppression of gene expression which is also dependent upon a high degree or at least a recognizable degree of sequence identity or homology between transgene and target sequence (Waterhouse P. *et al.,* Trends in Plant Sciences, November 1999, Vol. 4, No. 11 pp. 452-457; page 453 column 1 lines 32-40).

Given the lack of guidance in the instant specification, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified antisense or sense sequences, ribozymes or external guide sequences, either by testing non-exemplified fragments of SEQ ID NO: 1 or any other UDP-glucose dehydrogenase in sense or antisense orientation; or screening through the non-exemplified antisense RNA, non-exemplified ribozymes, or non-exemplified external guide sequences by producing transformation vectors and transforming plants therewith, in order to identify those anti-HGD nucleic acid molecules that when expressed in a plant would be useful for inhibiting the activity of homogentisate dioxygenase when expressed in a plant.

Therefore, given the breadth of the claims; the lack of guidance and working examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled throughout the broad scope of the claims.

Applicant asserts that the Branch article is about designing antisense as a drug and is not relevant to the field of plant biotechnology (response page 14). The general principles of nucleic

acid duplex biochemistry is the same whether it is a plant gene or from another species. Applicant has not proposed any explanation or mechanism to suggest otherwise.

Applicant asserts that the Bourque reference shows that antisense technology was well established in the before the priority date of the present invention (response page 15). Applicant's attention is directed to page 131 of the Bourque reference in column 1 end of section 4.2. The author states that UGPase antisense showed no effects upon metabolism even when UGPase activity was reduced to 4% of wild type. Moreover the reference is directed to using full length sequences which were state of the art when the reference was published in 1995 and does not support Applicant's remarks that the reference supports the use of fragment or anti-HGD sequences.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim without any active, positive steps delimiting how this method is actually practiced is indefinite.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 33, 42 and 43 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claimed inventions encompass untransformed seeds, which are a product of nature and not one of the five classes of patentable subject matter. Claims 33, 42 and 43 are drawn to seeds of the transformed plant. Due to Mendelian inheritance of genes, a single gene introduced into a parent plant would only be transferred at most to half the male gametes and half the female gametes. This translates into only two thirds of the progeny having at least a single copy of the transgene and one quarter of the progeny would not carry a copy of the transgene. Since the claim encompasses progeny that lack the transgene, the claim encompasses plants and seeds that are indistinguishable from plants and seeds that would occur in nature. See *American Wood v. Fiber Distintegrating Co.*, 90 U.S. 566 (1974), *American Fruit Growers v. Brogdex Co.*, 283 U.S. 2 (1931), *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 33 U.S. 127 (1948), *Diamond v. Chakrabarty*, 206 USPQ 193 (1980).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fernandez-Canon J. *et al.* The Journal of Biological Chemistry, 8 September 1995, Vol. 270, No. 36; pp. 21199-21205 in view of Tsegaye Y. *et al.* American Society of Plant Biologists, Annual Meeting Conference Abstracts; 1999, July 24 – July 28; See Transgenics and Biotechnology section, Abstract #413 and in further view of Applicant's admission of the prior art. This rejection is

maintained for the reasons of record set forth in the Official action mailed 12/30/2004. Applicant's arguments filed 7/05/2005 have been considered but are not deemed persuasive.

The claims are broadly drawn to a vector encompassing an expression cassette comprising an antisense homogentisate dioxygenase nucleic acid sequence having a HGD motif operably linked to a plant specific promoter or the 35S promoter, a microorganism comprising a vector encompassing an expression cassette comprising an antisense homogentisate dioxygenase nucleic acid sequence having a HGD motif, plants transformed with either the said vector or said microorganism comprising the said vector; and a method of transformation using said HGD nucleic acid sequence; wherein the office interprets a homogentisate dioxygenase (HGD) sequence motif in accordance with SEQ ID NO: 1 (a homogentisate dioxygenase nucleic acid sequence from *Brassica napus*) of Claim 6 as any HGD encoding nucleic acid sequence because any HGD encoding nucleic acid sequence would comprise a HGD sequence motif in accordance with SEQ ID NO: 1 and the cress plant of Claim 15 to encompass any cress plant species.

Fernandez teaches a recombinant cloning/expression vector cassette (pGEX-2T) comprising an antisense HGD nucleic acid sequence (*hmgA* from *A. nidulans*) designated as pGEX::AGMH transformed into *E. coli* on page 21202; beginning in column 1, line 5 to column 2, line 12, and thus the reference teaches all the limitations of Claims 1-2, 6-7 and 10.

Fernandez does not teach a recombinant vector comprising a 35S or plant specific promoter and an OCS terminator functionally linked to an anti-HGD nucleic acid and a host microorganism comprising said recombinant vector; a plant transformed with said vector or said host microorganism comprising said recombinant vector, and a method of transforming a plant with either the vector or the host microorganism comprising the vector.

Tsegaye teaches transformation of *Arabidopsis* (i.e. Thale cress, a cress species) with a recombinant vector construct comprising either a plant specific seed promoter DC3 or a 35S promoter operably linked to an antisense homogentisate dioxygenase cDNA (HGA-dioxygenase) from *Arabidopsis* that encompasses a homogentisate dioxygenase (HGD) sequence motif in accordance with SEQ ID NO: 1 in antisense orientation.

Applicant's specification teaches that the prior art discloses polynucleotide sequences encoding homogentisate dioxygenase enzymes from human, mouse and *Arabidopsis* (page 15 lines 41-44 of the specification); transformation methods comprising *Agrobacterium tumefaciens* meditated transformation and a biolistic plant transformation (in the specification, end of page 12 to middle of page 13); the 35S promoter and OCS terminator (specification page 18 lines 26-31); the legumin B promoter (specification page 17 lines 11-13); and a method of transforming *Brassica napus* using *Agrobacterium tumefaciens* (specification, in Example 5 pages 19-20).

It would have been obvious at the time of invention to modify the bacterial anti-HGD expression cassette of Fernandez to substitute a 35S promoter or plant specific promoter and an OCS terminator for *Agrobacterium tumefaciens* mediated transformation of *Arabidopsis* to express an anti-HGD in a plant as taught by Tsegaye and the prior art recited in Applicant's specification. One of ordinary skill in the art would have been motivated by the knowledge common in the art that an anti-HGD expression construct operably linked to the 35S promoter or a seed specific DC3 promoter are valuable materials for studying tocopherol production in plants and for genetically engineering plants to have greater tocopherol biosynthesis as taught by Tsegaye, and that *Agrobacterium* mediated transformation as taught by Applicants specification is easily applied to a wide range of plants including *Arabidopsis*, and that one would have had a

reasonable expectation of success of transforming *Arabidopsis* or other crop plants and selecting for transformed plants, plant cells, and tissues in view of the success of Tsegaye, wherein incorporating *Agrobacterium tumefaciens* mediated transformation into a method of increasing.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Russell Kallis Ph.D.
September 20, 2005

RUSSELL P. KALLIS, PH.D.
PATENT EXAMINER

Russell Kallis